

RESPONSE TO OFFICE ACTION

A. Status of the Claims

Claims 12-13, 15-27, and 33-34 were pending in view of the present Action and the Restriction Requirement dated October 1, 2007. Claims 1-11, 14, 28-32, and 35-55 were withdrawn. As noted below, it is requested that claims 28-30 also be acknowledged as being linked to claim 12. Claims 26 and 28 are amended as requested in the Action. No new matter has been added. Thus, claims 12-13, 15-30, and 33-34 are presented herein for reconsideration.

B. Status of Election/Restriction Requirement

The Action has acknowledged Applicant's election of Group III (claim 15). Applicants note that in this Action claims 28-30 were apparently withdrawn as drawn to a non-elected group or species, in spite of the previous Action's acknowledgement, for instance, that claim 12 was considered as a linking claim. Applicants note that claims 28-30 depend ultimately on claim 12 and include all of its limitations. Applicants thus respectfully request that claims 28-30 also be acknowledged as being linked by claim 12, and be examined upon allowability of claim 12.

C. Claims Rejections Under 35 U.S.C. § 112, First Paragraph

The Action rejects claims 12 and 15 under 35 U.S.C. § 112, first paragraph, as failing to comply with the Written Description Requirement. For instance, the Action at pages 4-10 cites MPEP 2163 and lists factors to be used to determine whether sufficient evidence of possession of the invention is furnished in the Application disclosure. The eight factors listed are essentially those of *In re Wands* (MPEP 2164.01). However, the factors of *In re Wands* relate to the Enablement Requirement, and not to the Written Description Requirement. Thus, the reasoning of the Action is

unclear, and withdrawal of the rejection, or its reformulation to allow a further response, is respectfully requested. However, to the extent possible, Applicants respond below.

Regarding the Written Description Requirement, the Office has the initial burden of presenting evidence or reasons why a person skilled in the art would not recognize that the written description of the invention provides support for the claims. MPEP 2163. However, the Action provides no reasoning demonstrating a *prima facie* lack of Written Description. On the contrary, all reasoning provided in this section of the Action relates instead to the Enablement Requirement. Applicants also submit that an actual reduction to practice is disclosed in the Specification as filed. For instance, the Specification at page 5, line 26, Example 2B and in FIG. 10 shows inhibition of absorption of cholesterol by Caco-2 cells in the presence of a “HMF” fraction with oil body associated proteins (“OBAP +”), while no such inhibition is found when the cells are cultured in the presence of isolated soy protein (“SPI”) lacking oil body associated protein (*i.e.* “OBAP -”). Preparation of “OBAP +” and “OBAP -” protein fractions is also described in Example 4. Because no *prima facie* case has been made, Applicants respectfully request that the rejection in view of the Written Description Requirement be withdrawn.

Given the reasoning provided in this section of the Action, Applicants also attempt to respond to the rejection as being due to an asserted lack of enablement. That is, the factors considered in the Action at pages 4-10 are essentially those listed as undue experimentation factors relating to enablement (MPEP 2164.01(a), the *In re Wands* factors).

Regarding the asserted factors, Applicants note that the Specification provides more than adequate direction and guidance for the skilled artisan to make and use the claimed invention without undue experimentation. For instance, numerous compositions for treating hypercholesterolemia are provided (*e.g.* Table 1). The formulated compositions comprise isolated

soy material, such as the high molecular fraction (“HMF”) of soy protein isolate, or purified glycinin and/or β -conglycinin, as well as isolated oil body associated protein (“OBAP”) such as oleosin(s) and fragments of oleosins. Numerous methods to prepare HMF, glycinin and β -conglycinin fragments, oleosin, and oleosin fragments are described in Example 1, resulting for instance in the polypeptides and fragments of Tables 2-3. The effect on cholesterol uptake of isolated soy material, both purified and thus reduced in or lacking OBAP, as well as when in the presence of OBAP are described in Example 2, and in FIG. 10. Importantly, a dose dependent effect on cholesterol uptake of an isolated HMF enriched in oil body associated protein (OBAP +) is shown in FIG. 10, while a fraction of soy material tested with only low amounts of OBAP (“Soy Protein Isolate” as described at page 5, line 26) shows no such effect. Therefore, Applicants respectfully submit that the assertion of the Action at page 9 that “the specification does not provide any examples of formulations displaying synergy, cholesterol lowering, or hypercholesterolemia treatment” is not accurate. A novel mechanism of action for inhibition of cholesterol uptake, distinct from that of sitostanol, is also described, in Example 3 and FIG. 11. The Action acknowledges at page 7 that multiple fragments of β -conglycinin are described. In total, the Specification provides clear guidance for one of skill in the art to combine soy fractions with OBAP to achieve a synergistic (*i.e.* combined; see definition below) effect in lowering cholesterol levels.

Studies on methods and compositions for treating hypercholesterolemia are well known, for instance as evidenced by the numerous references cited in the Action. Regarding “predictability” in the art, Applicants submit that it is not necessary to show that all possible embodiments work as claimed. Rather, the Specification provides a working example demonstrating the synergistic effect of, for instance, HMF and OBAP, in reducing cholesterol absorption, along with numerous teachings regarding isolation and formulation of various compositions and fractions of soy material

comprising soy polypeptides and oil body associated proteins. Therefore, further experimentation is not undue.

Applicants also respectfully submit that, in spite of the assertion in the Action at page 5, “cholesterol” and “neutral fat” are not equivalent terms, but are distinct in the art. This is shown, for instance, in the cited reference by Kohno, in Tables 4-5, wherein levels of each of “neutral fat” and “cholesterol” are reported separately. However, the Action apparently considers the terms to be equivalent (*e.g.* Action, page 5, paragraph beginning “(3) *Level of skill...*”). Thus, Kohno is mischaracterized.

The Action also cites to references by Berenbaum, published respectively in 1977 and 1989. As these references were published approximately 13-25 years before the priority date, they cannot accurately represent the state of the art at the time of filing. Indeed, the Action’s apparent understanding of the term “synergy” is puzzling. Applicants submit that the term “synergy” may be defined for instance according to the Merriam-Webster Online Dictionary (<http://www.merriam-webster.com/dictionary/synergy>) as “combined action or operation”. The meaning of this is self-evident and clear to one of skill in the art.

D Claim Objection

The Action objects to claims 26-27 because of informalities asserted with regards to dependence on claim 20. The Action further states that claims 28-30 would have been included in the objection “if they were not withdrawn as being (drawn to a) non-elected species.” Applicants note in response that claims 26 and 28 have been amended. The objection is therefore moot, and its withdrawal is respectfully requested.

E. Claims Rejections Under 35 U.S.C. § 103(a)

1. In view of Kohno, Yamada, and Berenbaum

The Action rejects claims 12, 15-19, 26-27, and 34 as being unpatentable over Kohno (WO 02/26243; English equivalent EP 1 323 425 A1), in view of Yamada *et al.* (PNAS 86:665-669, 1989) and further in view of Berenbaum (1977) and Berenbaum (1989). Applicants respectfully traverse.

The Kohno reference explicitly relates to purifying the 7S globulin (*i.e.* β -conglycinin), to remove “contaminating” oil-body-associated proteins (*e.g.* Kohno, paragraph 0008 at page 2). This is acknowledged by the Action at page 5, section (3) wherein it is stated that the effect (of 7S globulin) in reducing cholesterol is “enhanced when oil-body proteins...are removed.” Further, the Action at page 11, middle of last paragraph, also characterizes Kohno as disclosing that “further removing a membrane protein rich oil-body-associated protein, which contaminates a soybean protein [sic] the efficacy of the 7S globulin...is enhanced.” In contrast, the present results show that soy proteins provide a cholesterol-lowering effect when ingested in conjunction with oil body associated proteins, and the presently claimed effect is entirely unexpected in view of Kohno. Additionally, at page 6, last two lines, the Action explicitly states that “Kohno provides a teaching away from 7S globulin with oil-body proteins providing synergy.” Because, as acknowledged by the Action, the present disclosure provides unexpected results in view of Kohno, and Kohno clearly teaches away from the presently claimed invention, which relates to preparation and use of compositions enriched in OBAP, the logical basis for the rejection in view of the Kohno reference is flawed, and the rejection can not stand. The addition of numerous other references (Yamada, Hori, Lovati, Manzoni, Liu, Kelly, Fiordaliso, Wojcicki) in various combinations, as is made in the Action, does not cure this defect (see below). Withdrawal of the rejection is respectfully requested.

Applicants also note later publications (Kambara *et al.*; *Kenkou Eiyou Shokuhin Kenkuyuu; J. Nutr. Food* 7:1-19, 2004; translation provided; and Kohno *et al.* *J. Athero. and Thromb.* 13:247-255, 2006) which both include Kohno as a co-author, and show that purified 7S globulin (β -conglycinin) had no effect on total serum cholesterol (e.g. see Kambara Table 5, and page 8, section (2); and see Kohno (2006) at Table 4A). In total, the effect observed by Kohno in their patent application (EP 1 323 425 A1) was apparently due to contaminating molecules, such as OBAP, that were present in their preparations. When more highly purified materials were used, no effect on serum cholesterol was observed. This, in the final analysis, further shows the inventive nature of the present invention, which may be summarized as disclosing that 7S globulin serves to lower cholesterol when ingested in the presence of oil body associated proteins or lipoproteins.

The Action also cites a reference by Yamada *et al.* (*PNAS* 86:665-669, 1989). Applicants respond by noting that the Yamada reference does not relate to describe use of any glycinin or β -conglycinin as is presently claimed. Instead, use of a lipoprotein by itself is taught. Thus, the reference would not clearly lead one of skill in the art to combine apoE with any other composition, and there would have been no expectation of success in using any such combination of apoE and another ingredient. Indeed, given the teaching of Kambara that 7S globulin is not efficacious for lowering serum cholesterol (by itself), there would be no reason to combine this globulin with apoE. Further, the reference does not cure the defects of the Kohno reference that are outlined above, regarding the effects of 7S globulin. Thus, Applicants respectfully request withdrawal of the rejection.

Regarding the Berenbaum references, it appears that the Action considers the term “synergy” to be unclear. Applicants respectfully submit that this aspect of the rejection is more properly a clarity rejection, rather than an obviousness rejection. Applicants further submit that the

Berenbaum references, published 16-28 years prior to the present filing date, do not represent the state of the art at the time of filing. However, as noted above, Applicants submit that the term “synergy” may be defined for instance according to the Merriam-Webster Online dictionary (<http://www.merriam-webster.com/dictionary/synergy>) as “combined action or operation”. Applicants also note that the Berenbaum reference does not cure the defect of the Kohno reference in that Kohno teaches away from the present invention. Withdrawal of the rejection insofar as it is made on the basis of the Berenbaum references is thus respectfully requested.

2. In view of Kohno, Yamada, Berenbaum, and Hori

Hori (*Biosci Biotechnol. Biochem.* 65:72-78, 2001) is cited in rejecting claims 12-13, 15, 20, 24, and 26-27, as teaching another cholesterol-lowering ingredient, a soy protein hydrolyzate with bound phospholipids, in that two compositions each of which is taught by the prior art to be useful for the same purpose, may be combined to form a third composition. MPEP 2144.06. Applicants respectfully traverse. Applicants respectfully note that the presently claimed invention is not taught or suggested by Kohno, Yamada, or Berenbaum, and Hori does not cure this defect, or show how the disclosure of Kohno leads to the present invention. At most, Hori is cumulative of Yamada, or vice versa, in describing a cholesterol-lowering ingredient that is distinct from those presently claimed, and does not relate to a synergistic effect of glycinins in conjunction with OBAPs. Withdrawal of the rejection is respectfully requested.

3. In view of Kohno, Yamada, Berenbaum, Lovati, and Manzoni

Lovati (*J. Agric. Food Chem.* 46:2474-2480, 1998) and Manzoni (*J. Agric. Food Chem.* 46:2481-2484, 1998) are cited in rejecting claims 12, 15, 26-27, and 33, as disclosing the ability of different soy globulins to alter metabolism of cholesterol carriers and/or activate cellular lipoprotein receptors, resulting in possibly reduced cholesterol levels. Applicants respectfully traverse, in that

these teachings relate only to effects of soy globulins, and not to any effects of using OBAP in conjunction with a globulin. In these references, the possible effects of soy globulins are being studied, but oil body associated proteins and effects are simply not mentioned. Thus, the references do not teach or suggest the presently claimed invention, or lead one of skill in the art to it. Withdrawal of the rejection is respectfully requested.

4. In view of Kohno, Yamada, Berenbaum, and Liu

Liu (U.S. 5,968,516) is cited regarding claims 12, 15, 20-22, 26-27, as teaching that soybean saponins can decrease serum lipids, and that it would have been obvious to add the saponins of Liu to β -conglycinin and apoE compositions. Applicants respectfully traverse. Applicants can discern no teachings of Liu that would lead one of skill in the art to the presently claimed invention relating to use of OBAPs in conjunction with glycinin and/or β -conglycinin, or fragments thereof. Applicants also submit that the Liu reference is not relevant to claims 12 and 15, 21-22, and claims 26-27 as currently amended, which do not recite use of saponins. The basis for the rejection at least of these claims is thus unclear, and is unsupported. Regarding claim 20, Liu does not cure the defects of Kohno or the other cited references as discussed above. Withdrawal of the rejection is respectfully requested.

5. In view of Kohno, Yamada, Berenbaum, and Kelly

Claims 12, 15, 20-22, 26-27 are rejected over Kohno, in view of Yamada, Berenbaum, and Kelly (U.S. 5,830,887). Kelly is cited as disclosing use of phytoestrogens, flavones *etc.* Applicants respectfully traverse. First, Applicants note that these teachings are not relevant to claims 12, 15, or 26-27 as amended, which do not recite such compounds. Regarding claims 20-22, Kelly does not cure the defect of Kohno, which teaches away from use of globulins in conjunction with OBAPs. Withdrawal of the rejection is respectfully requested.

6. In view of Kohno, Yamada, Berenbaum, and Fiordaliso

Claims 12, 15, 20, 23, and 26-27 are rejected as obvious over Kohno and further in view of Yamada, Berenbaum, and Fiordaliso (*Lipids* 30:163-167, 1995). Applicants respectfully traverse. Fiordaliso apparently relates to administration of a carbohydrate (oligofructose) to lower cholesterol. Applicants note that these teachings are not relevant to claims 12, 15, or 26-27 as amended, which do not recite such compounds. Regarding claims 20 and 23, Fiordaliso does not cure the defect of Kohno, which teaches away from use of globulins in conjunction with OBAPs. Withdrawal of the rejection is respectfully requested.

7. In view of Kohno, Yamada, Berenbaum, and Wojcicki

Claims 12, 15, 20-22, and 26-27 are rejected as obvious over Kohno and further in view of Yamada, Berenbaum, and Wojcicki (*Phytotherapy Res.* 9:597-599, 1995). Wojcicki apparently relates to use of lecithin to lower cholesterol. Applicants note that these teachings are not relevant to claims 12, 15, 21-22, or 26-27 as amended, which do not recite such compounds. Regarding claim 20, which recites "phospholipid" which could include lecithin, Wojcicki does not cure the defect of Kohno, which teaches away from use of globulins in conjunction with OBAPs. Withdrawal of the rejection is respectfully requested.

F. Conclusion

In view of the above, it is submitted that all of the rejections to the claims have been overcome, and the case is in condition for allowance.

The Examiner is invited to contact the undersigned at (214) 259-0931 with any questions, comments, or suggestions relating to the referenced patent application.

Respectfully submitted,

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